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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/520,130	03/07/2000	Robert Arathoon	P1099R2	1353

23552 7590 02/22/2007

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/520,130	ARATHOON ET AL.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/06, 12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed 11/30/2006 is acknowledged. Claims 47-63 are examined on the merits.

Claim Rejections Withdrawn:

2. The provisional rejection of claims 47-63 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 88-109 of copending Application No. 09/863,693 is withdrawn in view of the abandonment of 09/863,693.

3. The rejection of claims 47-52 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment to the claims so that the claims are not drawn to bispecific antibodies that comprise two binding sites, each binding to different antigens, where the variable domain of the light chain of each binding site is the same.

4. The rejection of claims 59, 60, and 63 under 35 U.S.C. 102(b) as being anticipated by Hu (Hu, S. et al., Cancer Res. 56: 3055-3061, 1996) is withdrawn in view of the amendment to claim 59 to limit the claims to bispecific antibodies wherein the first and second binding domains bind to different antigens.

New Rejection—Necessitated by Amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 53 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 53 is indefinite because the phrase "the first and second light chain variable domains" lack antecedent basis in claim 47, from which it depends.

Claim Rejections Maintained:

Double Patenting

6. The provisional rejection of claims 47-63 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-38, 40-43, 45- 51 and 53-55 of copending Application No. 09/373,403 is maintained for the reasons of record. Applicants have indicated that upon an indication of allowable subject mater, a terminal disclaimer may be filed, if appropriate.

7. The provisional rejection of claims 47-63 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 45-82 of copending Application No. 10/143,437 is maintained for the reasons of record. Applicants have indicated

that upon an indication of allowable subject mater, a terminal disclaimer may be filed, if appropriate.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 47, 52, and 53 remain rejected under 35 U.S.C. 102(b) as being anticipated by Nissim (Nissim, A. et al., The EMBO Journal, 13(3): 692-698, 1994; cited in IDS) as evidenced by Merchant (Merchant, A.M. et al, Nature Biotechnology, 16: 677-681, 1998; cited in IDS).

Nissim teaches methods for expressing scFv fragments in *E. coli* from a phage library. Merchant teaches that the phage library of Nissim is library that has extensive H chain repertoires and unique L chain sequence, thus each antibody fragment derived from the phage library of Nissim has the same L chain (see page 677, 1st column). Nissim also teaches the making of "polyclonal" supernatants, which appear to be supernatants that contain scFv fragments with multiple specificities. In addition, Nissim teaches that dimerization occurs in the supernatants, especially when the supernatant has been concentrated (see 695, 2nd column). Nissim teaches that for polyclonal scFv fragments, the supernatant was concentrated. The dimerization appears to occur through the binding of an L chain region from one chain binding to

an H chain region from another chain. Therefore, Nissim inherently teaches the claimed bispecific antibodies and compositions comprising said antibodies.

The rejection has been withdrawn for claims 54 and 58, which have been amended to claim bispecific antibodies further comprising multimerization domains that each comprise a C_H3 region of an antibody constant domain. The rejection is maintained for claims 47, 52 and 53. Applicants' arguments have been carefully considered but fail to persuade. Applicants argue that Nissim fails to teach a method making bispecific antibodies that comprise a multimerization domain. However, in the broadest interpretation, the bispecific antibodies of claims 47, 52 and 53 do not necessarily comprise separate multimerization domains. Therefore, these claims read on diabodies where the interaction between the two scFvs is through the interaction of the heavy and light chain variable domains. Diabodies are formed by the binding of a light chain variable domain from one scFv binding with a heavy chain variable domain of a second scFv, and the binding of the light chain variable domain from the second scFv with the heavy chain variable domain of the first scFv. Therefore, it appears that Nissim's "polyclonal" multimerized products are bispecific, and because Nissim uses an scFv library with only one light chain, the products are the same as that claimed.

9. Claims 47, 48, 50, 52, and 53 remain rejected under 35 U.S.C. 102(b) as being anticipated by de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13): 7630-7634, 1996, March) as evidenced by Merchant (supra).

de Kruif teaches a method for making bispecific scFv antibodies that contain IgG3 hinge regions and either a Fos or Jun leucine zipper to the scFv proteins. To increase stability of the

bispecific antibodies, cysteine residues are incorporated into the leucine zippers, facilitiating disulfide bridge formation. The nucleic acid encoding the dimerization regions (IgG3 together with the leucine zippers and cysteine residues) are dimerization cassettes that are introduced into the NotI restriction sites of genes encoding scFvs isolated from a variety of phage display libraries, such as Nissim (see page 7632, 2nd column). Merchant provides evidence that the library of Nissim is a library that has extensive H chain repertoires and unique L chain sequence. Thus, each antibody fragment derived from the phage library of Nissim has the same L chain (see page 677, 1st column). Therefore, de Kruif provides bispecific antibodies that are the same as that claimed.

Applicants' arguments have been considered, but fail to persuade. Applicants argue that de Kruif fails to teach bispecific antibodies comprising C_H3 domains. However, claims 47, 48, 50, 52 and 53 are not limited to antibodies comprising multimerization domains that are C_H3 domains. Applicants also argue that de Kruif fails to teach an example of a bispecific antibody with a common light chain. This is not found persuasive because de Kruif does teach making bispecific antibodies from phage libraries such as that of Nissim, which is a library that has an extensive H chain repertoire and a unique L chain sequence. Therefore, inherently any bispecific antibody made from the Nissim library would be a bispecific antibody that has a common light chain.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 47-49, 52-55, 58-61 and 63 remain rejected under 35 U.S.C. 103(a) as being unpatentable over de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13): 7630-7634, 1996, March) as evidenced by Merchant (supra) in view of Ridgeway (of record) for the reasons of record.

Claims 47-49, 52, 54, 55, 58-61 and 63 include within their scope, bispecific antibodies that contain engineered C_H3 domains, where the first and second polypeptides interact at an

amino acid side chain protuberance of one polypeptide and an amino acid side chain cavity of the other polypeptide. The protuberance and cavity interaction as a means to promote heavy chain heterodimerization is not taught by de Kruif. However, such heterodimerization methods are known in the art as evidenced by the teachings of Ridgeway, which teaches the "knobs-into-holes" strategy, which is a method for altering the C_H3 domain of the heavy chain of a bispecific antibody. Ridgeway teaches that this method has been used to successfully enhance the production of bispecific diabodies (page 620, last paragraph). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made have altered the constructs of de Kruif by using the "knobs-into-holes" method for the purpose of dimerizing the bispecific scFv constructs of de Kruif.

Applicants' arguments have been considered, but fail to persuade. Applicants assert that none of the references teaches a bispecific antibody comprising a common light chain, and that therefore, the combination of references fails to teach or suggest the claimed bispecific antibodies. This is not found persuasive because de Kruif teaches making antibodies from a phage library where all of the scFv fragments comprise a common light chain. This interpretation of de Kruif is based on the teaching of de Kruif that bispecific antibodies may be made from the phage library of Nissim (explained above). What de Kruif fails to teach is heterodimerization using engineered C_H3 domains. Instead de Kruif teaches heterdimerization using Fos and Jun leucine zippers. However, as explained in the previous Office action, heterodimerization of bispecific antibodies using engineered C_H3 domains is known in the art as evidenced by the teachings of Ridgeway, and Ridgeway teaches that this method has been used successfully to enhance production of bispecific antibodies (page 620, last paragraph).

Therefore, one of ordinary skill in the art would have the means and motivation to make bispecific antibodies using the method of Ridgeway to introduce engineered C_H3 domains because Ridgeway teaches that this method enhances production of bispecific antibodies. Therefore, the combination of references teaches the claimed inventions, and furthermore the teachings of Ridgeway provides motivation for making bispecific antibodies having engineered C_H3 domains because Ridgeway teaches that such a method improves heterdimerization.

11. Claims 47- 63 remain rejected under 35 U.S.C. 103(a) as being unpatentable over de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13): 7630-7634, 1996, March) as evidenced by Merchant (supra) in view of Ridgeway (of record) and further in view of Hu (Hu, S. et al., Cancer Res. 56: 3055-3061, 1996) for the reasons of record.

The combination of de Kruif and Ridgeway teach as set forth above. The combination fails to teach bispecific antibody constructs where the non-naturally occurring disulfide bond is between the C_H3 multimerization domains of the first and second polypeptide. However, Hu teaches that single chain Fv constructs can be made divalent by fusing the single chain antibody chains with C_H3 regions (see page 3056, Figure 1); and also teaches the "flex minibody" in which the C_H3 is fused to a hinge region, which contains cysteines for the formation of disulfide bonds, which further stabilize the dimmer (see page 3059, 1st column). Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified de Kruif's bispecific antibodies to have a C_H3 multimerization domain with knobs and holes mutations as taught by Ridgeway, and further to have added hinge region to the C_H3 region so that disulfide bonds could form between the heterodimers.

Applicants argue that the combination of references fails to teach or suggest the claimed inventions. This argument is not found persuasive because de Kruif teaches making antibodies from a phage library where all of the scFv fragments comprise a common light chain. This interpretation of de Kruif is based on the teaching of de Kruif that bispecific antibodies may be made from the phage library of Nissim (explained above). What de Kruif fails to teach is heterodimerization using engineered C_H3 domains that also comprise a non-naturally occurring disulfide bond between the C_H3 domains. However, as explained in the previous Office action, the formation of disulfide bonds in a multimerization domain for the purpose of stabilizing a dimmer is known in the art as evidenced by the teaching of Hu (see above). Therefore, one of ordinary skill in the art would be motivated to make the claimed bispecific antibodies that comprise non-naturally occurring disulfide bonds because Hu teaches that benefits of such bonds for the stabilization of antibody dimer constructs.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
February 19, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER